[CONTRIBUTION FROM THE RESEARCH LABORATORY OF RALPH L. EVANS ASSOCIATES]

Pyridoquinoxalines

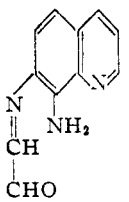
BY FRED LINSKER AND RALPH L. EVANS

The growing importance of nitrogen ring bases to the pharmaceutical industry is well indicated by the steadily increasing number of heterocyclic sulfa-drugs, antimalarial compounds, and general germicidal agents. Sulfapyrazine[1] and sulfaquinoxaline[2] have already met considerable success and the search for new bactericidal and plasmodicidal derivatives of quinoline and acridine continues unabated.

The purpose of this investigation was to produce new heterocyclic nuclei of a condensed pyridine-quinoxaline type, of which the nitro- and amino-substitution products could be used for the synthesis of new chemotherapeutic agents. Of the eight possible pyridoquinoxalines, three can also be designated as quinolinopyrazines; theoretically, therefore, these would be accessible through condensation of the appropriate diaminoquinolines with glyoxal. None of these possible reactions has been reported previously, although the more complex condensation products of 5,6-diaminoquinoline[3] and 7,8-diaminoquinoline[4] with phenanthrenequinone have been prepared. The preparation of 3-hydroxy-pyrido(3,2-f)quinoxaline-2-carboxylic acid from 5,6-diaminoquinoline and mesoxalic acid[5] has also been described.

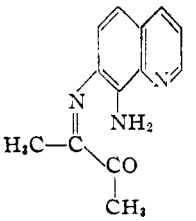
Of our attempts to form simple quinoxalines from 5,6- and 7,8-diaminoquinoline, only the first was successful. In the case of the 7,8-diamino compound both glyoxal and diacetyl condensed with only one amino group and the ring was not closed. This may be explained by the weakly basic character and consequently low reactivity of the amino group in position 8. A comparison of the relative basicity of 7-aminoquinoline and 8-aminoquinoline in 0.25% aqueous solution showed *p*H values of 8.67 and 7.05, respectively. The formation of dinitrophenylhydrazones and N-acetyl derivatives established the structures I and II for the condensation products.[6]

(I)



7-(8-Aminoquinolyl)-iminoacetaldehyde

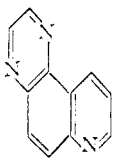
(II)



7-(8-Aminoquinolyl)-imino-2-butanone

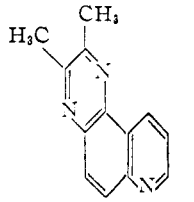
Pyrido(3,2-f)quinoxaline (III) and its 2,3-dimethyl derivative (IV) were obtained in fair yields from the condensation of 5,6-diaminoquinoline with glyoxal and with diacetyl, respectively.

(III)



Pyrido(3,2-f)quinoxaline

(IV)



2,3-Dimethylpyrido-(3,2-f)quinoxaline

These are colorless crystalline compounds which are soluble in dilute mineral acids. When treated at reflux temperature with a solution of hydrogen peroxide in glacial acetic acid, N-oxides are formed. It was of interest to observe that the unsubstituted compound yielded the tri-N-oxide, whereas the dimethyl derivative gave a di-N-oxide under identical conditions.

Experimental

6-Aminoquinoline.—The 6-nitroquinoline used as starting material was made by Knueppel's method; yield 72%, m. p. 150–151° (lit. yield 70%[7]; m. p. 148–149°[8]). As reduction of 6-nitroquinoline in alcoholic medium[9] was not satisfactory, the following process was used: 100 g. of 6-nitroquinoline was dissolved in 500 cc. of glacial acetic acid and 500 cc. of water was added to the solution. This solution was warmed to 60° and 80 g. of iron powder was added slowly with mechanical stirring. After the reduction was completed, the mixture was cooled in an ice-bath and made alkaline adding solid sodium carbonate with mechanical agitation. After standing in the refrigerator for two hours, the precipitate was filtered, washed, and dried in partial vacuum. The dry, powdered mass was extracted repeatedly with ether, refluxing each time for two hours. The combined ether extracts were dried with sodium sulfate. After the solvent was evaporated, the residue of 80 g. of crude 6-aminoquinoline remained. This was distilled at 10–13 mm. pressure and 187–200°, yielding 70 g. (85%) of the pure base, m. p. 114° (lit.[10] 114°).

6-Tosylaminoquinoline.—The reaction of 6-aminoquinoline with *p*-toluenesulfonyl chloride in C.P. pyridine yielded 87% of the crude condensation product. A previous investigator[5] obtained a yield of 96% when using dry pyridine as a solvent. The product was recrystallized from alcohol; m. p. 193–194° (lit.[9] 193°).

5-Nitro-6-tosylaminoquinoline.—6-Tosylaminoquinoline was nitrated according to the procedure of Kaufmann and Zeller.[3] It proved essential to use recrystallized, finely powdered tosylaminoquinoline. This was added in small

(1) Ellingson, THIS JOURNAL, **63**, 2524 (1941).

(2) Weijlard, Tishler and Erickson, *ibid.*, **66**, 1957 (1944).

(3) Kaufmann and Zeller, *Ber.*, **50**, 1626 (1917).

(4) Renshaw, Friedman and Gajewski, THIS JOURNAL, **61**, 3325 (1939).

(5) Rudy, *Ber.*, **71**, 847 (1938).

(6) The ring formation between 7,8-diaminoquinoline and phenanthrenequinone is explained by the greater reactivity of the latter toward α,β-diamines in general; for example, dibenzoquinoxaline is readily formed from phenanthrenequinone and ethylenediamine. The latter is not known to yield cyclic compounds with glyoxal or diacetyl.

(7) Knueppel, *Ber.*, **29**, 705 (1896).

(8) Le Fèvre and Le Fèvre, *J. Chem. Soc.*, 1472 (1935).

(9) Knueppel, *Ann.*, **310**, 76 (1900).

(10) Hargreaves, Marshall and Whorton, *J. Am. Pharm. Assoc.*, **28**, 140 (1939).

portions with mechanical stirring to 3 parts of 60% nitric acid. During the addition, the temperature should not exceed 70° and thereafter the mixture should be kept at 60–70° for two hours. Under these conditions the yield in several runs amounted to 85–90% of the theoretical (lit.[5] 60–80%). After one recrystallization from alcohol the product melted at 166° (lit.,[3] 168–169°).

5-Nitro-6-aminoquinoline.—The method described in the literature[3,5] was somewhat improved when the nitrotosylamino compound was slowly stirred into concentrated sulfuric acid to avoid local overheating. Yields varying from 85–90% were obtained regularly. Recrystallized from toluene the base melted at 174° (lit.[5] 174°).

5,6-Diaminoquinoline.—To a suspension of 5 g. of 5-nitro-6-aminoquinoline in 33 cc. of 10 normal hydrochloric acid was slowly added in small portions a solution of 32 g. of stannous chloride dihydrate in 45 cc. of concentrated hydrochloric acid. The mixture was heated on the steam-bath and 175 cc. of 3-normal hydrochloric acid was added, producing a clear solution. After being heated for an hour, the solution was placed in the refrigerator overnight to permit crystallization of the tin double salt. The latter was filtered, washed with a little water, dissolved in normal hydrochloric acid, and hydrogen sulfide was passed through this solution. The precipitated sulfide was removed by filtration and the tin-free filtrate was evaporated to dryness on a steam-bath. Five grams (81%) of 5,6-diaminoquinoline dihydrochloride was obtained; m. p. 279–283° (lit.[3] 280–285°).

Pyrido(3,2-f)quinoxaline (III).—Thirty-seven grams of 5,6-diaminoquinoline dihydrochloride was dissolved in 110 cc. of water and to this solution was added a solution of 48 g. of glyoxal sodium bisulfite compound in 185 cc. of warm water. The reaction mixture was warmed to 50–60° for fifteen minutes in a water-bath, then cooled, and made strongly alkaline by the addition of 10 *N* sodium hydroxide. The alkaline mixture was extracted exhaustively with ethyl acetate and the extract was dried with sodium sulfate. The solvent was evaporated, leaving 15 g. (52%) of fairly pure pyrido(3,2-f)quinoxaline as residue. The base formed colorless leaflets which melted at 135°. It is readily soluble in dilute mineral acids and alcohol; less soluble in water and ethyl acetate; insoluble in ligroin. The picrate was prepared in alcoholic medium and recrystallized from water. It formed small yellow needles which sintered at 132° and melted at 165–166°.

Anal. Calcd. for $C_{11}H_7N_3 \cdot C_6H_3O_7N_3$: C, 49.7; H, 2.4. Found: C, 49.2; H, 2.8.

Pyrido(3,2-f)quinoxaline Tri-N-Oxide.—Two grams of pyrido(3,2-*f*)quinoxaline was dissolved in 20 cc. of glacial acetic acid and 10 g. of 100-vol. hydrogen peroxide was added. The solution was heated for two hours to reflux temperature, diluted with 150 cc. of water, neutralized with 30% caustic soda solution, and then allowed to crystallize in the refrigerator. The precipitate was filtered, washed with a little water, and dried over calcium chloride in a partial vacuum; yield 1 g. When recrystallized from dilute acetic acid, the product formed tan prisms; m. p. > 400°.

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.6; H, 3.1. Found: C, 57.6; H, 3.0.

2,3-Dimethyl-pyrido(3,2-f)quinoxaline (IV).—2.5 g. of 5,6-diaminoquinoline dihydrochloride was dissolved in 30 cc. of *N*/3 sulfuric acid. To this solution was added 1 g. of diacetyl and the mixture was heated for fifteen minutes in a boiling water-bath. After cooling, an excess of ammonium hydroxide was added, the precipitate was allowed to settle and was then filtered, washed with 10 cc. of water, and dried; yield, 2.0 g. (89%). The product was recrystallized from boiling water and dried at 20 mm. and 100°, yielding a microcrystalline powder which melted at 142–144°.

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.7; H, 5.3. Found: C, 74.6; H, 5.4.

2,3-Dimethyl-pyrido(3,2-f)quinoxaline Di-N-oxide.—A solution of 2 g. of dimethylpyridoquinoxaline in 20 cc. of glacial acetic acid and 10 g. of 100-vol. hydrogen peroxide was boiled for two hours under reflux. The cooled reaction mixture was then poured into 80 cc. of water, placed in an ice-bath, and neutralized by slowly adding 30% sodium hydroxide solution with stirring. After standing overnight, the precipitated di-N-oxide was filtered, washed with water, and dried *in vacuo;* yield, 2 g. (87%). When recrystallized from ethanol, tan needles, m. p. 255–257°, were obtained. They were readily soluble in hot water, hot alcohol, and dilute mineral acids; sparingly soluble in cold water and alcohol; insoluble in ether, benzene, and chloroform.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.8; H, 4.6. Found: C, 65.1; H, 4.5.

7,8-Diaminoquinoline Dihydrochloride.—This compound was obtained from 7-aminoquinoline through a series of reactions analogous to those described for the preparation of the 5,6-isomer and reported in detail in a previous note.[11]

7-(8-Aminoquinolyl)-iminoacetaldehyde (I).—A solution of 2.4 g. of glyoxal bisulfite in 10 cc. of hot water was added to a solution of 1.8 g. of 7,8-diaminoquinoline dihydrochloride in 6 cc. of hot water. The mixture was warmed to 50–70° for thirty minutes in a water-bath, then cooled, made alkaline by an excess of 40% caustic soda solution. After standing overnight, the precipitate was filtered, washed with water, and dried over calcium chloride in a desiccator; yield, 1.5 g. (97%) of crude product which after recrystallization from dilute alcohol formed clusters of fine yellow needles; m. p. 219–220°.

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.3; H, 4.5. Found: C, 66.5; H, 4.4.

The 2,4-dinitrophenylhydrazone was obtained as orange platelets; m. p. 274°.

7-(8-Acetylaminoquinolyl)-iminoacetaldehyde.—0.5 gram of 7-(8-aminoquinolyl)-iminoacetaldehyde was dissolved in 2 cc. of acetic anhydride and the solution was refluxed for one hour; 10 cc. of water was added and the solution was boiled for several minutes to eliminate the excess of acetic anhydride. The mixture was cooled and filtered and the filtrate was made alkaline while being cooled externally. The precipitated acetyl compound was filtered, washed with water, and recrystallized from alcohol as orange platelets, m. p. 174–176°.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.73; H, 4.56. Found: C, 65.38; H, 4.58.

7-(8-Aminoquinolyl)-imino-2-butanone (II).—1.2 cc. of diacetyl was added to a solution of 3 g. of 7,8-diaminoquinoline dihydrochloride in 40 cc. of 0.5 *N* sulfuric acid. The mixture was heated for thirty minutes in a boiling water-bath, cooled, and alkalized by an excess of 40% sodium hydroxide solution. After remaining in the refrigerator overnight the precipitate was filtered, washed with water, and dried over calcium chloride; 2.7 g. (95%) of crude reaction product was obtained. When recrystallized from ethyl acetate–ligroin, this formed clusters of yellow prisms; m. p.138–140°.

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.8; H, 5.7. Found: C, 68.9; H, 5.3.

The 2,4-dinitrophenylhydrazone crystallizes in dark brown plates, m. p. 245°.

7-(8-Acetylaminoquinolyl)-imino-2-butanone.—One gram of 7-(8-aminoquinolyl)-imino-2-butanone was heated with 4 cc. of acetic anhydride for one hour at reflux temperature; 20 cc. of water was added and after boiling for fifteen minutes more, the solution was cooled and filtered. An excess of caustic soda solution was then added to the externally cooled filtrate. The precipitate was separated, dried, and recrystallized from benzene and ligroin; small orange prisms; m. p. 137–138°.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.58. Found: C, 66.86; H, 5.30.

(11) Linsker and Evans, THIS JOURNAL, **68**, 149 (1946).

Acknowledgment.—The authors wish to express their appreciation to Miss Mildred Howson for her valuable assistance.

Summary

1. 5,6-Diaminoquinoline was prepared from 6-nitroquinoline through several improved steps.

2. Pyrido(3,2-f)quinoxaline and 2,3-dimethylpyrido(3,2-f)quinoxaline were synthesized. The former yielded a tri-N-oxide whereas the latter formed only a di-N-oxide when heated with a solution of hydrogen peroxide in acetic acid.

3. Tricyclic systems could not be obtained from 7,8-diaminoquinoline with glyoxal or diacetyl. The condensation stopped at the iminoaldehyde and iminoketone, respectively. Both condensation products were identified.

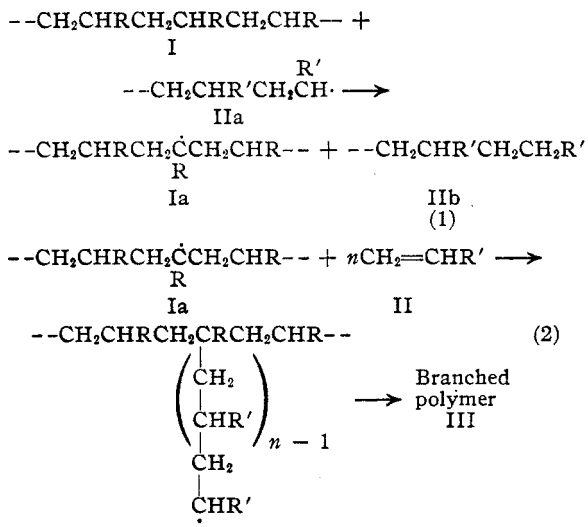
250 EAST 43RD STREET
NEW YORK 17, N. Y. RECEIVED JANUARY 28, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Polymerization of *p*-Chlorostyrene in the Presence of Polymethylacrylate

BY ROBERT B. CARLIN AND NANCY E. SHAKESPEARE

The first indication that a polymer molecule, in the presence of growing polymer chains, may be capable of increasing its molecular size was provided by the experiments of Houtz and Adkins.[1] Their viscosity measurements led them to conclude that new styrene units may attach themselves to polystyrene molecules when the latter are subjected to the action of polymerizing monomer. Flory[2] suggested that branched vinyl polymers could result from chain transfer reactions involving polymer molecules (I) and growing polymer chains (IIa)



It is apparent that Flory's mechanism could account for the results reported by Houtz and Adkins. Mayo[3] presented experimental evidence that growing polymer chains engage in chain transfer reactions with solvent molecules; and a comparison of the activities of various solvents in the chain transfer reaction prompted Mayo to propose that growing polymer chains could also undergo chain transfer reactions with polymer molecules as Flory had suggested. It appeared likely that growing polymer chains could undergo chain transfer not only with polymer molecules composed of the same monomer units (equations 1 and 2, R = R′) but also with polymer molecules composed of different monomer units (R ≠ R′). If such is the case, then branched chains (III) should be formed in which the principal chain is composed of units of one kind and the branch of units of another kind. If the polymer (I) and the monomer (II) which is to form the growing chains (IIa) are selected in such a way that polymers I and IIb have widely differing solubility characteristics, then it should be possible to separate completely one or the other of the polymers from the branched molecules (III). If, further, either R or R′ contains a group which can be detected by analytical methods, then the presence of III can be established after I or IIb has been separated from the polymer mixture. This paper reports a preliminary investigation of the polymerization of *p*-chlorostyrene (II, R′ = pC_6H_4Cl) in the presence of polymethylacrylate (I, R = $COOCH_3$). The polymer mixture which presumably contained I, IIb and III was saponified in order to convert polyacrylate chains into polyacrylic acid chains (I and III, R = COOH), and the product was extracted with benzene, in which IIb is soluble, and I (R = COOH) insoluble. It was anticipated that the branched polymer, if present, (III, R = COOH, R′ = C_6H_4Cl) would be substantially insoluble in benzene so that its presence could be detected by analysis of the insoluble material for chlorine.

In order that a maximum number of chain transfer reactions of the type represented by equation 1 could occur in the polymerizing mixture, experimental conditions were so chosen that other types of chain transfer reactions were minimized. Since solvents have been shown to serve as chain transfer agents,[3] the polymerizations were carried out in bulk. Inasmuch as growing chains presumably may be terminated by coupling or disproportionation reactions, both of

(1) Houtz and Adkins, THIS JOURNAL, **55**, 1609 (1933).
(2) Flory, *ibid.*, **59**, 241 (1937).
(3) Mayo *ibid.*, **65**, 2324 (1943).